PERFORMANCE OF A1C VERSUS OGTT FOR THE DIAGNOSIS OF PREDIABETES IN A COMMUNITY-BASED SCREENING

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Abstract

Objective—Reliable identification of individuals at risk for developing diabetes is critical to instituting preventative strategies. Studies suggest that the accuracy of using A1c as a sole diagnostic criterion for diabetes may be variable across different ethnic groups. We postulate that there will be lack of concordance between A1c and the Oral Glucose Tolerance Test (OGTT) for diagnosing prediabetes across Hispanic and Non-Hispanic White (NHW) populations.

Research Design and Methods—218 asymptomatic adults at risk for Type 2 Diabetes (T2D) were assessed with A1c and OGTT for the diagnosis of prediabetes. Glucose homeostasis status was assigned as no diabetes (A1c < 5.7%), prediabetes (A1c 5.7% – 6.4%), and T2D (A1c > 6.4%). Inclusion criteria were age > 18 years and at least one of the following: a family history of diabetes, a history of gestational diabetes, Hispanic ethnicity, non-Caucasian race, or obesity. Subjects received a fasting 75-gram OGTT and A1c on the same day. Bowker's Test of Symmetry was employed to determine agreement between the tests.

Results—Data from 99 Hispanic patients and 79 NHW patients were analyzed. There was no concordance between A1c and OGTT for Hispanic (p=0.002) or NHW individuals (p=0.003) with prediabetes.

Conclusions—A1c is discordant with OGTT among Hispanic and NHW subjects for the diagnosis of prediabetes. Sole use of A1c to designate glycemic status will result in a greater prevalence of prediabetes among Hispanic and NHW New Mexicans.

Key Terms

prediabetes; diagnosis; screening; oral glucose tolerance test; A1c

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Introduction

The prevalence of prediabetes and T2D is rapidly growing in the United States. The Center for Disease Control and Prevention's (CDC) 2014 National Diabetes Statistics Report states that 35% of non-Hispanic Whites (NHW) and 38% of Hispanics over 20 years of age have pre-diabetes.[1] In New Mexico, 7.8% of the population has pre-diabetes.[2] In 2009, Herman et al. found that A1c was higher among Hispanics with T2D when compared to NHW with T2D even after adjusting for factors known to affect glycemia.[3] Furthermore, multiple studies have shown disparities in A1c between Hispanics and NHW with diabetes.[4,5] A reliable method for identifying prediabetes and diabetes is essential for optimal patient care and for prevention of diabetes-related microvascular complications. Since the American Diabetes Association and the International Expert Committee adopted A1c criteria for the diagnosis of diabetes in 2009, there has been controversy regarding the diagnostic usefulness of this test because the A1c test may have limitations such as moderate sensitivity for diagnosing diabetes when compared to OGTT.[3,6–14] Even so, few studies have evaluated the diagnostic ability of this test for diagnosing prediabetes as opposed to overt diabetes. We undertook a study to evaluate the diagnostic performance of A1c compared to OGTT in the minority-majority state of New Mexico, whose population consists of approximately 47% Hispanics, 39% NHW, 10% Native American, and 4% other ethnicities.[15] We hypothesized that there would be a lack of concordance for the designation of prediabetes between A1c and OGTT amongst Hispanic and NHW populations in New Mexico.

Research Design and Methods

The study was approved by the UNM Human Research Review Committee and all participants rendered written informed consent. Using a combination of clinic flyers, workplace notifications, convenience sampling, and word of mouth promotion, we recruited nominally nondiabetic subjects living in Albuquerque, NM who were unaware of their diabetes status. Subjects were required to be 18 years of age or older with at least one of the following risk factors: a family history of type 2 diabetes in a first degree relative, a history of gestational diabetes, Hispanic ethnicity, non-Caucasian race, or obesity (BMI $\geq$ 30 kg/m^2). A total of 218 adults were recruited. All subjects received a medical history and physical examination and completed a comprehensive health status questionnaire that allowed self-designation of race and ethnicity. Patients were instructed to eat a normal diet and to have normal physical activity for at least three days prior to the appointment for the OGTT according to WHO recommendations.[16] A 75 gram oral glucose tolerance test (OGTT) was performed in the fasting state between 0700 and 0900.[17] A hemoglobin A1c (A1c) test was obtained on the same morning. Subjects were classified according to glucose

homeostasis status as follows: no diabetes, A1c < 5.7%; prediabetes (incorporating both impaired fasting glucose and impaired glucose tolerance), A1c = 5.7% – 6.4%; and diabetes (T2D), A1c > 6.4%.

Plasma glucose and A1c were assayed at a central laboratory. The method used to analyze plasma glucose samples was a UV hexokinase assay. This method is College of American Pathologists (CAP) certified, with a coefficient of variation ranging from 2.26–2.59%. A1c was determined using HPLC on a Tosoh G8 analyzer and follows the guidelines of the National Glycohemoglobin Standardization Program (NGSP). The assay was CAP certified, and the coefficient of variation for A1c was 1.3%.

Bowker's Test of Symmetry was used to determine agreement for the designations of no diabetes, prediabetes, and diabetes between A1c and the 75 gram OGTT. This test assesses statistical agreement between two variables with more than two categories, with perfect agreement designated by a p-value of 1.0. The Hispanic and NHW groups were analyzed separately to determine if there was a difference in agreement between these two ethnicities. Sensitivity and specificity of the A1c test were also determined for each ethnic group using the OGTT as the gold standard. We derived the Pearson correlation coefficient between A1c and fasting glucose, as well as between A1c and 2 hour OGTT glucose. Finally, we compared OGTT and A1c using McNemar's chi-squared test.

Results

Table 1 presents the baseline characteristics of study participants. We recruited 99 Hispanic subjects, 79 NHW subjects, and 40 subjects of other racial and ethnic groups (10 African Americans, 2 North Africans, 21 Native Americans, 1 of mixed Native American- Hispanic-English heritage, 5 Asians, and 1 Persian). Forty-five percent of our study population was Hispanic. There was a significant difference in age between the Hispanics and NHW (p<0.01), with the Hispanics being younger than the NHW. Furthermore, a larger proportion of the study population was female (p<0.01). BMI was similar across all ethnicities. Of the 218 participants, 104 (48%) were designated with prediabetes based on their A1c.

Table 2 shows the glycemic status according to OGTT versus A1c for Hispanic subjects (n=96). Three patients with incomplete laboratory data were excluded from the analysis. Thirty Hispanic participants were classified as having no diabetes by the OGTT but as having prediabetes by A1c, and 74 Hispanic subjects were classified as having no diabetes by the OGTT while only 51 participants were classified as having no diabetes by the A1c. Eighteen subjects were classified as having prediabetes by the OGTT classification, while 45 subjects were classified as having prediabetes by A1c. Bowker's Test of Symmetry for Hispanics returned a p-value of 0.002, indicating poor agreement between the tests. Furthermore, McNemar's chi-squared test comparing OGTT and A1c for Hispanics with no diabetes and those with prediabetes returned a p-value of 0.0001, demonstrating that there is a significant difference between these two tests for the diagnosis of prediabetes. The sensitivity of A1c was 67% (95% Confidence Interval [CI] = 42%–85%) and the specificity was 60% (95% CI= 49%–71%) compared to the OGTT among Hispanic participants.

Table 3 shows glycemic status according to OGTT versus A1c among the NHW participants (n=79). Twenty-six individuals were classified as having no diabetes by the OGTT but as having prediabetes by A1c criteria, while 58 NHW subjects were classified as having no diabetes by the OGTT, compared to 37 subjects who received this classification by A1c criteria. Similarly, 18 subjects were designated as having prediabetes by OGTT criteria, while 40 subjects were designated as having prediabetes using the A1c criteria. Bowker's Test of Symmetry returned a p-value of 0.003 for this analysis, indicating poor agreement between the tests. In addition, McNemar's chi-squared test comparing A1c and OGTT between NHW with no diabetes and those with prediabetes revealed a p-value of 0.003, demonstrating a significant difference between A1c and OGTT for the diagnosis of prediabetes. A1c had a sensitivity of 71% (95% CI= 47%–87%) and a specificity of 55% (95% CI= 43%–67%) compared to the gold standard OGTT among NHW individuals.

Figure 1A shows the Pearson correlation between A1c and fasting plasma glucose with a correlation coefficient (r) of 0.49. Figure 1B shows the Pearson correlation between A1c and the 2 hour OGTT glucose, with a correlation coefficient of 0.32.

Discussion

The findings of our study raise questions regarding the utility of the A1c test to screen for prediabetes in community based screening efforts. When the ADA and the International Expert Committee proposed the A1c as a diagnostic criterion for diabetes, the A1c test was heavily scrutinized and found to possess many beneficial attributes as compared to the OGTT.[18] Specifically, the A1c reflects chronic hyperglycemia better than OGTT, even if the OGTT is performed on repeated occasions.[19] Additionally, A1c is more predictive of microvascular complications of diabetes, such as diabetic retinopathy, nephropathy, and neuropathy than is fasting plasma glucose.[7,18–20] It is these microvascular complications that increase patient morbidity, thus making early diagnosis and prevention critical to patient care. Our study is unique in that we focus on the diagnosis of prediabetes as opposed to T2D among at-risk patients with unknown glucose homeostasis status.

While the A1c and OGTT have many benefits as a diagnostic tests, there are also drawbacks to these testing modalities. For example, A1c is a surrogate marker for long-term glycemic control that measures protein glycation instead of measuring blood glucose directly.[19] As such, multiple blood pathologies can affect the A1c, including hemoglobinopathies, erythrocyte abnormalities, acute blood loss, pregnancy, and iron deficiency.[7, 19] There are drawbacks to the OGTT as well. In addition to the need for patient preparation prior to the test, there is lack of within-patient reproducibility from test to test among individual patients due to intra-individual variation.[9,19] The pathophysiology of diabetes involves the body's inability to maintain euglycemia in both the postprandial and fasting states, and the OGTT primarily evaluates postprandial pathology better than the A1c.[19] The A1c also has poor sensitivity for diagnosing diabetes early in the course of dysglycemia, and in this instance, the OGTT may be better able to accurately diagnose such patients.[19–21] Nakagami et al. found that A1c was similar to FPG in evaluating diabetes risk.[22] We found a similar relationship in our study with a positive correlation between elevated fasting plasma glucose and elevated A1c (see Figure 1A).

There are diseases in which ethnic variability is important. The CDC recently published an MMWR report about the causes of death and prevalence of disease and risk factors in Hispanics.[23] They compared Hispanic, non-Hispanic whites, and Hispanic country/region of origin subgroups. Hispanics had higher death rates from diabetes, chronic liver disease and cirrhosis, essential hypertension and hypertensive renal disease and homicide. They also had higher prevalence of diabetes and obesity compared to whites. Based on such studies showing the importance of ethnicity with regard to disease prevalence and outcomes, we separated our study population by ethnicity to determine if there was ethnic variability with regard to the concordance between A1c and OGTT. Our study found no difference, as both Hispanics and NHW showed a comparable lack of agreement between A1c and OGTT for the diagnosis of prediabetes.

Using the A1c to diagnose diabetes has epidemiologic consequences amongst various ethnic groups.[19, 24] Current studies show differences in A1c by race and ethnicity among patients with impaired glucose tolerance.[3,5,6] In fact, A1c appears to run higher among minorities with impaired glucose tolerance. Furthermore, a meta-analysis of T2D patients who were Hispanic and NHW found that the A1c was 0.5% higher among Hispanics.[3] Another meta-analysis compared A1c values between NHW and African Americans and found that the A1c was 0.65% higher in this ethnic group.[25] As a result, it is possible that ethnic minorities will be diagnosed with prediabetes sooner than their NHW counterparts. In our study, we found the A1c test commonly diagnosed the patient with prediabetes among Hispanic participants while the OGTT diagnosed the patient with no diabetes. Although the A1c might over-diagnose prediabetes in ethnic minorities, this could have substantial clinical value since important lifestyle changes could be implemented earlier than if diagnosis was based solely on the OGTT.

Several studies have examined the sensitivity and specificity of A1c for the diagnosis of diabetes.[21,26] Some conclude that the A1c is "sensitive enough," while others maintain that it is relatively insensitive. One study that evaluated the accuracy of A1c in patients with Impaired Glucose Tolerance found that the A1c was not sensitive enough to be used for the routine diagnosis of T2D or Impaired Glucose Tolerance as compared to plasma glucose concentrations.[21] Many studies conclude that because of the discordance between A1c and OGTT, using both A1c and OGTT (or a fasting plasma glucose combined with clinical symptomology) produces the most accurate method for diagnosing diabetes and prediabetes.[7,26] In 2010, Lorenzo found that the combination of A1c and fasting plasma glucose detected 52.2% of the study participants with diabetes, as compared with 32.3% when A1c was used alone.[10]

Guo and colleagues found that A1c had a low sensitivity and high specificity for identifying diabetes and prediabetes.[28] They conclude that A1c values below 6.5% and 5.7% do not rule out the presence of diabetes and prediabetes, respectively. They suggested using fasting plasma glucose and 2-hour post-load blood glucose for diagnosing diabetes and prediabetes.[28] Yan and colleagues found that the diagnostic sensitivity and specificity of A1c for diabetes and prediabetes was improved when A1c and FPG criteria were combined.[26] The current study demonstrated moderate sensitivity and specificity of A1c in each group, so one approach might be to advocate that one test is not better than another in our population.

While our study verifies the lack of concordance between these two diagnostic modalities, we found that the sole use of A1c would result in a relative over-diagnosis of prediabetes as compared with the OGTT. Because the term prediabetes implies that an individual is at risk for the future development of overt diabetes, the effect of diagnosing prediabetes earlier, with a test like A1c, may result in improved prevention of overt diabetes. As a result, early detection might ultimately prevent or reduce the microvascular and macrovascular risks associated with dysglycemia.

Many factors have been found to have an effect on the diagnosis of prediabetes when A1c is used as the diagnostic method. Guo et al found increased rates of misdiagnosis with increased age and in NHW and Mexican Americans.[28] Yan et al also found that different A1c cut points were needed as age increased. For young and middle aged adults, the optimal A1c was 5.6% but for the elderly it was 5.7%.[26] James et al found that prediabetes prevalence varied by age, sex and ethnicity.[29] Finally, Li et al measured the effect of BMI on diagnosing prediabetes and found that with increasing BMI, the agreement between A1c and OGTT decreased.[30] The optimal cut points for prediabetes diagnosis in overweight subjects was 5.7% and 6.0% in obese subjects. When these values were used, the agreement between A1c and OGTT was similar to the agreement of normal weight subjects. These studies argue for A1c cut points for prediabetes that take ethnicity, BMI, and age into consideration.

Saukkonen and colleagues found differences in the prevalence of "intermediate hyperglycemia" when they compared A1c 5.7–6.4% to impaired fasting glucose (5.6–6.0 mmol/L) and impaired glucose tolerance (2-hour post-load glucose 7.8 and < 11.1 mmol/L).[31] The study by James and colleagues had similar findings.[29] Using NHANES data from 2005–2005 consisting of 3627 adults without known diabetes, the prevalence of prediabetes varied by the diagnostic criteria used. When A1c 5.7–6.4% was used, the prevalence was 14.2%. When FPG 100–125 mg/dL or FPG 110–125 mg/dL was used, prevalence was 26.2% and 7.0% respectively. When 2-hour OGTT values of 140–199 mg/dL were used, the prevalence was 14.7%.[29] Our study is consistent with these results, but it is likely that all of these studies evaluate different populations.

We included subjects over age 18 years who had at least one risk factor for diabetes. Our study describes a sample of convenience to the extent that subjects were recruited by word of mouth and through local clinics. It is interesting to note that the BMI of both the Hispanics and NHW subjects was similar, even though Hispanic ethnicity alone (with or without increased body mass index) would qualify such subjects for study (Table 1). According to the CDC, 28% of New Mexicans are obese and 36% are overweight.[32] The mean BMI of our subjects was 30.2 kg/m^2, so our study describes a relatively overweight or obese portion of the New Mexico population. Forty-six percent (46%) of our cohort had a BMI > 30 (obese), 25% had a BMI between 25–30 (overweight), and only 29% of our cohort had a normal BMI. Regarding the fact that Hispanics and NHW had similar BMI, it may be that people who were overweight or obese were more concerned about their risk of diabetes and so were more likely to volunteer for the study. We do not know for certain why there were not more Hispanic participants with a normal BMI in our study. In contradistinction to other studies, there was no correlation between BMI and A1C in the current study (r=0.29, p=0.69).[30, 33]

There are other limitations to our study. For example, the OGTT was performed on only one occasion, and current guidelines recommend that OGTT be performed on more than one occasion for improved accuracy.[17,34–36] It is thus possible that some of these participants were incorrectly categorized on the basis of a single test. But the current guidelines also stipulate that among individuals who exhibit discordant results upon repeat testing, "such patients will likely have test results that are near the margins of diagnostic threshold," and as such, should be followed closely with repeated testing in 3–6 months.[17] Accordingly, for the purposes of this study, we have chosen to interpret a single abnormal A1c or OGTT as indicative of some degree of glucose intolerance and dysglycemia that will require further monitoring and/or clinical intervention in the near future.

Additionally, our study was limited by its lack of inclusion of people with new, undiagnosed diabetes. The fact that only seven participants (3.2%) were identified with new diabetes reflects that this study was primarily designed to identify people with prediabetes. Indeed, if the medical community is to make an impact on the coming tide of patients with type 2 diabetes, intervention must be targeted at individuals with prediabetes.[37] Our study also had limited power, since we were only enrolled 218 subjects. Despite this limitation, our study shows that the A1c has sufficient sensitivity for the diagnosis of prediabetes. Further studies are needed to elucidate the differences in glycemic control amongst various ethnicities.

The purpose of our study was not to argue for the acceptance or rejection of the A1c as a diagnostic criterion for prediabetes. To do so would require a definitive test for the determination of prediabetes versus no prediabetes. There is uncertainty around the diagnosis of prediabetes due the "continuous variable" nature of blood glucose concentrations and the heterogeneous nature of prediabetes, including both impaired fasting glucose and impaired glucose tolerance.[38] The diagnosis of prediabetes is most useful when it designates either the stage at which an individual may begin to display hyperglycemic complications or a clear risk of progression to overt diabetes. For this reason, A1c may ultimately prove to be superior to the other methods of diagnosing prediabetes since it provides an integrated summary of prevailing glucose concentration over an extended period of time. The purpose of this report was to demonstrate that the relationship between A1c and fasting plasma glucose or post-challenge glucose concentrations is not a strict one. Much as is the case with the diagnosis of overt diabetes, the answer one gets when one is attempting to diagnose prediabetes appears to depend, to some degree, upon the test that is used to make the determination. Moreover, the lack of concordance between A1c and OGTT is no different for individuals of Hispanic ethnicity than for those of Non-Hispanic ethnicity.

In conclusion, our study shows lack of agreement between the A1c and OGTT for glucose homeostasis status among Hispanic and NHW adults from New Mexico. Current guidelines leave it to the clinician to use the criteria they choose to diagnose prediabetes and T2D. While there are limitations to both the OGTT and the A1c, studies continue to question how the A1c can best be used as a diagnostic test. Given the results of the current study, A1c criteria are most effectively employed with a clear understanding of how these results may vary with those obtained by other means. No matter how prediabetes is diagnosed, the importance of early detection and intervention must be emphasized to prevent unnecessary complications.

Acknowledgments

Abbreviations

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OGTT	Oral Glucose Tolerance Test
NHW	Non-Hispanic White
T2D	Type 2 Diabetes
UNM	University of New Mexico
NM	New Mexico
WHO	World Health Organization
HPLC	High Performance Liquid Chromatography
CAP	College of American Pathologists
CI	Confidence Interval
FPG	Fasting Plasma Glucose
BMI	Body Mass Index

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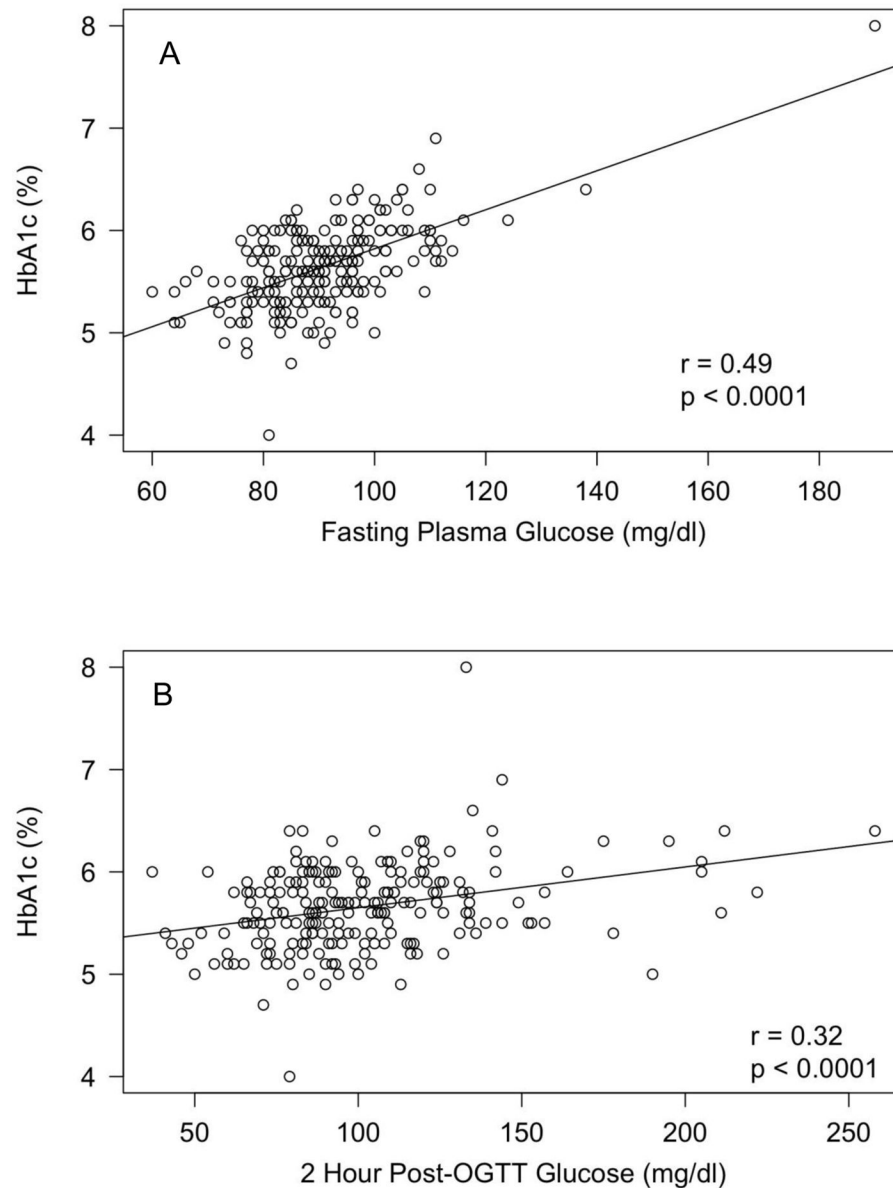
Figure 1.
Correlation between fasting plasma glucose and A1c (Panel A), and 2-hour post-load plasma glucose and A1c (panel B) during a standard 75 gram Oral Glucose Tolerance Test (OGTT). The line is an ordinary least squares fit to the data. The correlation r is the usual Pearson correlation coefficient; results were essentially identical using the Spearman correlation coefficient.

Table 1

Participant Demographics

	Hispanic	Non-Hispanic White	Other
Sample Size	99	79	40
Age (years)	40 ± 14	48 ± 14	40 ± 12
Gender (M,F)	24, 75	35,44	17,22
BMI (kg/m²)	30±8	30±6	31±7
Glycemic Status by A1c:			
Non-DM	51	37	20
Prediabetes	45	40	19
T2D	0	2	1
Glycemic Status by OGTT			
Non-DM	74	58	31
Prediabetes	18	18	9
T2D	4	3	0

Table 2

Hispanic Glycemic classification (n= 96)

	NonDM OGTT	Prediabetes OGTT	T2D OGTT
NonDM A1c	44	6	1
Prediabetes A1c	30	12	3
T2D A1c	0	0	0

Table 3

NHW Glycemic Classification (n= 79)

	NonDM OGTT	Prediabetes OGTT	T2D OGTT
Non-DM A1c	32	5	0
Prediabetes A1c	26	12	2
T2D A1c	0	1	1